Comparison of Estimated PCB-153 Concentrations in Human Milk Using Various Pharmacokinetic Models

David Farrer[1], Mike Poulsen[2], Dana Davoli[3], Marcia Bailey[3], Daphne Moffett[4], David Fowler[4], Clem Welsh[4], Ray Yang[5], Sami Haddad[6]

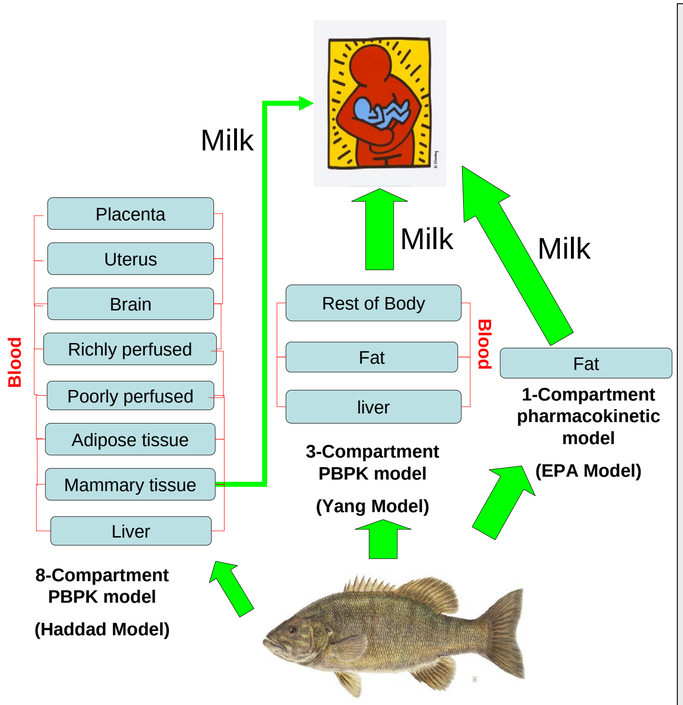
[1]Oregon Department of Human Services, [2]Oregon Department of Environmental Quality, [3]United States Environmental Protection Agency, [4]Agency for Toxic Substances and Disease Registry [5]Ray Yang Consulting LLC, Fort Collins, CO, 80526, [6]Dept. of Biological Sciences, TOXEN, Université du Québec à Montréal

Introduction

Background: Fish consumption can be a significant source of lipophilic contaminants, such as polychlorinated biphenyls (PCBs), that concentrate in human milk. In this respect, the nursing infant is at the pinnacle of the bioconcentration food chain. Risk to infants from consuming the milk of mothers who eat contaminated fish has not been quantitatively addressed in the fish advisory process. In the case of PCBs, EPA guidance for fish advisory programs uses the oral reference dose for Aroclor 1254 to establish the allowable fish consumption rate for children and adults who eat fish. This method does not account for the significant bioconcentration in the adipose of an expectant mother that will be mobilized and incorporated into breast milk. To adequately protect this most vulnerable population, the nursing infant, this dose from milk consumption should be considered when developing fish advisories and assessing risk at sites where lipophilic contaminants are present.

Obtaining human milk samples to measure contaminant concentrations is not practical in most cases, so it is desirable to have a method to estimate milk concentrations based on a lifetime average daily dose to the mother. Multiple models have been developed to produce these estimates. Here, we compare adaptations of 3 published models[1-3] as to their ability to predict human milk concentrations. The Haddad model is an 8-compartment physiologically-based pharmacokinetic (PBPK) model that has been validated by comparing estimated milk concentrations against concentrations measured in a Canadian Inuit population[1]. The Yang model is a 3-compartment PBPK model[2], and the EPA model is a single compartment, classical pharmacokinetic model[3].

We compared models by selecting 8 individuals from the data set provided by Sami Haddad who breast fed for at least 11 months and represented a representative spread of average daily doses of the PCB congener 153 (PCB-153). Simulated milk concentrations from each of the 3 models for the selected individuals were similar within a factor of 2. EPA's model, the simplest, consistently produced milk concentration estimates that were the highest of the 3 models but still within a factor of 2 (See Table 1 and Figures 1 and 2) of the validated Haddad model. This suggests that the EPA model is accurate and protective and may be a good choice for risk assessors and fish advisory practitioners.



Methods

- All three models consider eating contaminated fish as the environmental exposure pathway.
- Simulations were run using all three models to calculate the concentration of PCB-153 in milk after 6 and 12 months of breast feeding.
- Simulations also calculated average daily dose to infants via nursing.
- All three models started using maternal average daily doses for 8 individual Inuit women.
- Maternal average daily doses were back-calculated from measured blood concentrations using the Haddad model.

Table 1. Comparison of PCB-153 Concentrations in Milk Calculated from EPA Model, Haddad Model, and Yang Model

Subject ID	Dose to Mother ADDm (µg/kg/day)	6-Month Average Milk Concentration EPA (µg/kg-lipid)	6-Month Average Milk Concentration Haddad (µg/kg-lipid)	6-Month Average Milk Concentration Yang (µg/kg-lipid)	6-Month Concentration Ratios EPA/Haddad	6-Month Concentration Ratios EPA/Yang	6-Month Concentration Ratios Haddad/Yang	1-Year Average Milk Concentration EPA (µg/kg-lipid)	1-Year Average Milk Concentration Haddad (µg/kg-lipid)	1-Year Average Milk Concentration Yang (µg/kg-lipid)	1-Year Concentration Ratios EPA/Haddad	1-Year Concentration Ratios EPA/Yang	1-Year Concentration Ratios Haddad/Yang
1	0.0337	629	463	428	1.36	1.47	1.08	539	456	318	1.18	1.70	1.43
2	0.0154	286	153	194	1.88	1.47	0.79	246	135	144	1.82	1.70	0.94
3	0.0088	165	137	109	1.20	1.52	1.26	141	135	78	1.05	1.82	1.73
4	0.0075	140	79	94	1.78	1.49	0.84	120	72	70	1.66	1.72	1.03
5	0.0064	119	98	82	1.22	1.46	1.20	102	89	61	1.15	1.68	1.47
6	0.0057	106	53	74	1.99	1.45	0.73	91	50	55	1.84	1.67	0.91
7	0.0039	72	50	51	1.45	1.40	0.97	62	48	38	1.29	1.62	1.26
8	0.0015	28	14	19	2.00	1.47	0.74	24	13	14	1.87	1.69	0.90

Table 2. Comparison of PCB-153 Doses to Infant Calculated from EPA Model, Haddad Model, and Yang Model

Subject ID	Dose to Mother ADDm (µg/kg/day)	6-Month Average Dose to Infant EPA (µg/kg-BW/Day)	6-Month Average Dose to Infant Haddad (µg/kg-BW/Day)	6-Month Average Dose to Infant Yang (µg/kg-BW/Day)	6-Month Dose Ratios EPA/Haddad	6-Month Dose Ratios EPA/Yang	6-Month Dose Ratios Haddad/Yang	1-Year Average Dose to Infant EPA (µg/kg-BW/Day)	1-Year Average Dose to Infant Haddad (µg/kg-BW/Day)	1-Year Average Dose to Infant Yang (µg/kg-BW/Day)	1-Year Dose Ratios EPA/Haddad	1-Year Dose Ratios EPA/Yang	1-Year Dose Ratios Haddad/Yang
1	0.0337	3.16	2.110	1.84	1.50	1.71	1.15	2.13	1.709	0.92	1.24	2.31	1.85
2	0.0154	1.44	0.699	0.84	2.06	1.72	0.84	0.97	0.522	0.42	1.85	2.31	1.25
3	0.0088	0.83	0.627	0.47	1.32	1.77	1.34	0.56	0.506	0.23	1.10	2.47	2.24
4	0.0075	0.70	0.359	0.40	1.95	1.73	0.89	0.47	0.276	0.20	1.71	2.33	1.36
5	0.0064	0.60	0.448	0.35	1.34	1.70	1.27	0.40	0.342	0.18	1.18	2.29	1.94
6	0.0057	0.53	0.244	0.32	2.19	1.69	0.77	0.36	0.189	0.16	1.90	2.27	1.19
7	0.0039	0.36	0.227	0.22	1.59	1.64	1.03	0.24	0.181	0.11	1.35	2.21	1.63
8	0.0015	0.14	0.064	0.08	2.19	1.71	0.78	0.09	0.049	0.04	1.93	2.30	1.19

Figure 1

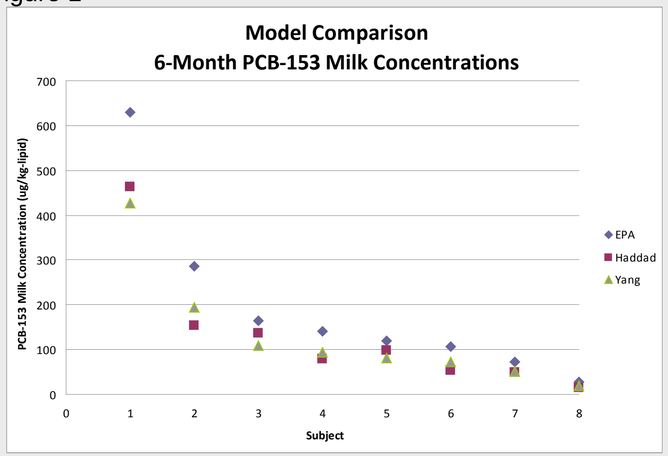
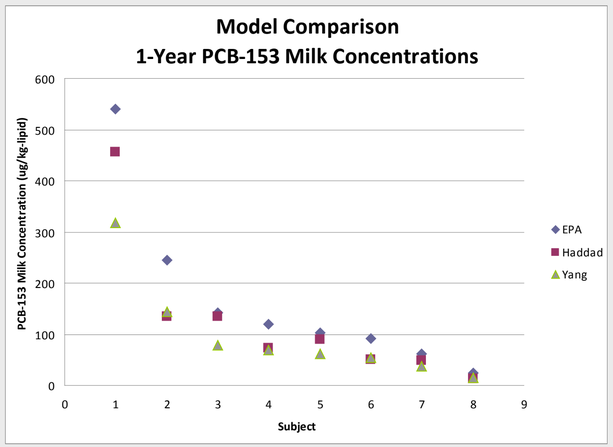


Figure 2



Conclusions

- Models can be used to estimate human milk concentrations.
- Estimated milk concentrations can be used to calculate oral dose to infants via human milk.
- These 3 models compared favorably and suggest that the EPA model may be the simplest and most health-protective model for use in risk assessment and fish advisory formulation.

References

1. Verner, M.A., et al., *A physiologically based pharmacokinetic model for the assessment of infant exposure to persistent organic pollutants in epidemiologic studies.* Environ Health Perspect, 2009. **117**(3): p. 481-7.
2. Redding, L.E., et al., *Population physiologically-based pharmacokinetic modeling for the human lactational transfer of pcb 153 with consideration of worldwide human biomonitoring results.* Environmental Health Perspectives, 2008(11519): p. 1-29.
3. Smith, A.H., *Infant exposure assessment for breast milk dioxins and furans derived from waste incineration emissions.* Risk Anal, 1987. **7**(3): p. 347-53.